

### R m rks

Claims 1, 2, 11-16, 18, 20-22, 24, 26, and 27 are pending in the present application. No additional claims fee is due.

Claims 1 and 12-14 have been amended. Support for the amendment to Claims 1 and 12-14 can be found at least on page 5 of the specification. Attached hereto is a marked-up version of the changes made to the claims by the current amendments. The attached page is captioned "Version with markings to show changes made."

### The Rejection under 35 U.S.C. 112, second paragraph

Claims 1, 2, 11-16, 18, 20-22, 24, 26, and 27 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite. Specifically, claims 1 and 12-14 have been rejected as reciting an ambiguous description regarding the deletion of positions. In response, Applicants have amended claims 1 and 12-14 to indicate that amino acids, rather than positions, be deleted at the positions corresponding to subtilisin BPN'. Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. 112, second paragraph has been overcome.

### The Double Patenting Rejection

Claims 1, 2, 11-16, 18, 20, 21, 24, and 26 have been provisionally rejected as claiming the same invention as that claimed in copending application 09/618,845. In response, Applicants are submitting herewith a Terminal Disclaimer addressing the application. Applicants contend that the Terminal Disclaimer moots the double patenting rejection.

### The Rejection under 35 U.S.C. 103(a) over Bryan et al.

Claims 1, 2, 11-16, 18, 20, and 22 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Bryan et al. (US 5,567,601). Applicants respectfully traverse this rejection, as there is no suggestion or motivation to modify the reference, as required by MPEP 2143.01. Bryan et al. teach the deletion of amino acids at the 70-74  $\alpha$ -helix together with the deletions of amino acids corresponding to amino acid positions 75-83 of the subtilisin BPN'. The present invention teaches deletion of one or more of positions 70-84 corresponding to subtilisin BPN', wherein the deletion is not 75-83. Therefore, a prima facie case of obviousness has not been established.

The Office Action states that it would have been obvious to delete fewer of the amino acids among the positions corresponding to positions 75-83 of subtilisin BPN' or to add further deletions to the most preferred deletion at the positions corresponding to positions 70-74 of subtilisin BPN'. While column 4 briefly mentions a deletion of any amino acid at positions 75-83, all other aspects of the invention specify a deletion in combination with the preferred deletion of 75-83. Further, it would not have been obvious to delete positions other than the most preferred deletions because Bryan et al. effectively taught away from such independent deletions by citing only examples with the deletions of positions 75-83. Column 9 and Table 1 describe specific mutants synthesized by Bryan et al., and all of the examples indicate that a deletion must be accompanied by the most preferred deletion of amino acids at positions 75-83. While a deletion of positions 70-74 of the  $\alpha$ -helix position may improve stability of the enzyme, it does so in combination with the preferred deletion of positions 75-83. Therefore, it would not have been obvious to create a subtilisin of the present invention, as Bryan et al. does not teach or suggest a deletion independent of a deletion of positions 75-83.

Furthermore, Applicants respectfully traverse this rejection, as there would be no motivation to modify the Bryan et al. teaching of subtilisin stability to the present invention's teaching of immune surveillance. Bryan et al. teach highly stable subtilisins that are independent of calcium, and therefore are more stable in the presence of metal chelators commonly found in industrial environments. The present invention teaches redesign of subtilisins to alleviate the immunogenic properties of an epitope region, thereby decreasing the immunological response. Thus, Bryan et al. teach protecting the protease from metal chelators, and the present invention teaches protecting the protease from a foreign immune system. The issues of subtilisin stability and immune surveillance are completely separate problems. One skilled in the art would have no motivation to modify Bryan's teachings of altering amino acids for the purpose of increasing subtilisin stability and result in the present invention's teachings of redesigning subtilisins to alleviate the immunogenic properties that cause immunological responses.

While both Bryan and the present invention teach protection of the protein, the mechanisms in achieving the protection are clearly different and therefore, one of ordinary skill in the art would not have been motivated to modify the Bryan reference. One skilled in

the art interested in the teachings of Bryan would be focused on protecting the protease from high concentrations of metal chelators. Bryan discloses a method of modifying serine protease enzymes to eliminate calcium binding in order to create mutated subtilisin enzymes that are more stable in the presence of metal chelators. Bryan does not teach or suggest that this method could be enhanced or applicable to any other form of protease protection. Therefore, one skilled in the art would have no motivation to modify the teachings of Bryan to create subtilisins that evoke a decreased immunological response.

Thus, the obviousness rejection given in the Office Action does not establish a *prima facie* case of obviousness. Therefore, Applicants contend that the claimed invention is unobvious and that the rejection should be withdrawn.

The Rejection under 35 U.S.C. 103(a) over Bryan et al. and Powell et al.

Claims 24 and 26 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Bryan et al. and Powell et al. (US 6,060,546). Applicants respectfully traverse this rejection because there is no motivation to combine the references, as required in MPEP 2143.01.

There is no motivation to combine Bryan et al. with Powell et al.. Powell et al. only teach the preparation of a personal care composition comprising subtilisin SP 544, while Bryan et al. specifically teach subtilisin deletion and modifications. One skilled in the art would not be motivated to combine a reference teaching specific deletions and modifications of specific regions of different subtilisins with the Powell et al. general description of a personal care composition comprising subtilisin SP 544. Bryan et al. specifically teach altering amino acids in subtilisin BPN' to increase stability with metal chelators. Powell et al. teach that subtilisins can be used in personal care compositions, and there would be no motivation to combine that broad and general teaching with a reference teaching inhibition of proteolysis in an industrial environment.

Therefore, Applicants contend that a *prima facie* case of obviousness has not been established, and the claimed invention is not obvious in view of the cited references.

The Rejection under 35 U.S.C. 103(a) over Bryan et al. and Arbige et al.

Claim 21 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Bryan et al. and Arbige et al. (EP 0 260 105). Applicants respectfully traverse this rejection because there is no motivation to combine the references, as required in MPEP 2143.01.

There is no motivation to combine Bryan et al. with Arbige et al.. Arbige et al. teach modifying nzymes with catalytic triads in order to alter the transesterification rate/hydrolysis rate ratio when the enzymes are used as a catalyst, while Bryan et al. teach subtilisin deletion and modification related to increasing stability in the presence of metal chelators. One skilled in the art would not be motivated to combine a reference teaching modification related to increasing stability with the Arbige et al. description of altering the transesterification rate/hydrolysis rate ratio. Bryan et al. specifically teach altering amino acids in subtilisin BPN' to increase stability with metal chelators. Arbige et al. teach that enzymes act as a catalyst by creating competing types of reactions including hydrolysis (acting on an ester form an alcohol and an acid) or transesterification (replace the ester with a different ester). There would be no motivation to combine the Arbige et al. teaching of alteration of nucleophile specificity in order to improve the use of enzymes in synthetic reactions with a reference teaching inhibition of proteolysis in an industrial environment.

Therefore, Applicants contend that a *prima facie* case of obviousness has not been established, and the claimed invention is not obvious in view of the cited references.

#### Conclusion

Applicants have made an earnest effort to place their application in proper form and to distinguish the invention as now claimed from the applied references. WHEREFORE, Applicants respectfully request reconsideration of this application, entry of the amendments presented herein and allowance of Claims 1, 2, 11-16, 18, 20-22, 24, 26, and 27.

Respectfully submitted,  
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**VERSION WITH MARKINGS TO SHOW CHANGES MADE****In the claims:**

Please amend claims 1, 12, 13, and 14 as follows:

1. A variant of a serine protease having a modified amino acid sequence of a wild-type amino acid sequence, wherein the modified amino acid sequence comprises a deletion of an amino acid at one or more of positions 70 – 84 corresponding to subtilisin BPN', wherein the variant is not  $\Delta$  75 – 83 or  $\Delta$  71.
12. A variant according to Claim 11 wherein the deletion of an amino acid is at is of one or more of positions 73-83 corresponding to subtilisin BPN'.
13. A variant according to Claim 11 wherein the deletion of an amino acid is at is of one or more of positions 70 and 75-82 corresponding to subtilisin BPN'.
14. A variant according to Claim 13 wherein the deletion of an amino acid is at is of one or more of positions 75-82 corresponding to subtilisin BPN'.